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PREDICTORS OF POOR OUTCOME (HIGH USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS) AT YEAR 1 FOLLOWING TOTAL KNEE/HIP ARTHROPLASTY: THE PRESS-UP COHORT STUDY

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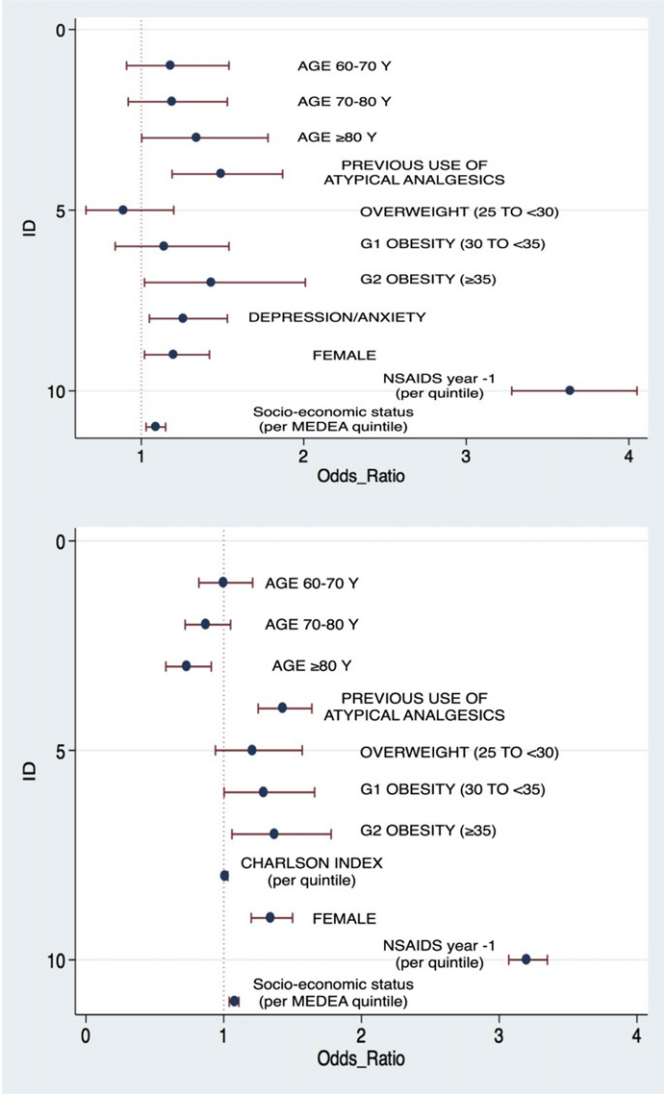
Purpose: Implant survival is the most accepted measurement of total knee (TKA) or hip arthroplasty (THA) results. There is a need for short-term surrogates for revision for both research and monitoring purposes. We have shown that highest utilisation of non-steroidal anti-inflammatory drugs (NSAIDs) in the first year following surgery is related to increased revision risk, and hence a useful surrogate for "poor outcome". We therefore aimed to identify predictors of high NSAID use at year 1 after TKA and THA surgery.

Methods: Study design and population: We used data from the Catalan Joint Registry (RACAT), and linked it (85% linked) to computerized primary care records and pharmacy invoice data (SIDIAP Database). We identified patients aged >=40 years undergoing primary TKA/THA for osteoarthritis registered in the resulting dataset in the period 1/1/2005-31/07/2012). We excluded patients receiving revision surgery in the first year post-surgery.



- Outcome assessment: NSAID utilisation was measured using pharmacy invoice data, and quantified in number of Daily Defined Doses (DDDs) according to the WHO ATC/DDD index. We classified patients in the top quintile (percentile 80 and over) of utilisation as those with a "poor outcome".
- Potential predictors: we defined a priori a set of predictors of poor outcome based on previous knowledge and biological plausibility, including: age, sex, socio-economic status, Charlson co-morbidity index, alcohol drinking, smoking status, body mass index, stroke/TIA, ischaemic heart disease, peripheral artheriopathy, depression/anxiety disorders, type 2 diabetes mellitus, previous fracture, chronic kidney failure, COPD, use of atypical analgesics (gabapentin, pregabalin or trycyclic antidepressants) in the previous year, use of NSAIDs in the previous year.
- Analysis: Backwards stepwise logistic regression (p-entry 0.05, p-exit 0.1) models were fitted to identify predictors of good outcome (as defined above).

Results: 22,221 and 10,173 patients undergoing TKA and THA for osteoarthritis were included. Female sex, lower socio-economic status, obesity, previous use of atypical analgesics, and amount of NSAIDs used in the year prior to surgery were associated with "poor outcome" in both THA and TKA patients [Figure, top and bottom respectively]. Conversely, Charlson co-morbidity index had an effect on poorer outcome for TKA patients, and a history of depression/anxiety disorders was related to poorer outcome following THA, but had no significant effect on the other subpopulation.

Conclusions: We report for the first time on a set of predictors of "poor outcome" as defined on the basis of NSAID usage during the first year following TKA surgery. A predictive tool can be built using these in order to target patients who would benefit the least from this surgical procedure. A validated version of such tool would be of interest for patients, clinicians and health-care managers.

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BISPHOSPHONATE USE AND IMPROVED IMPLANT SURVIVAL: A NATION-WIDE COHORT STUDY

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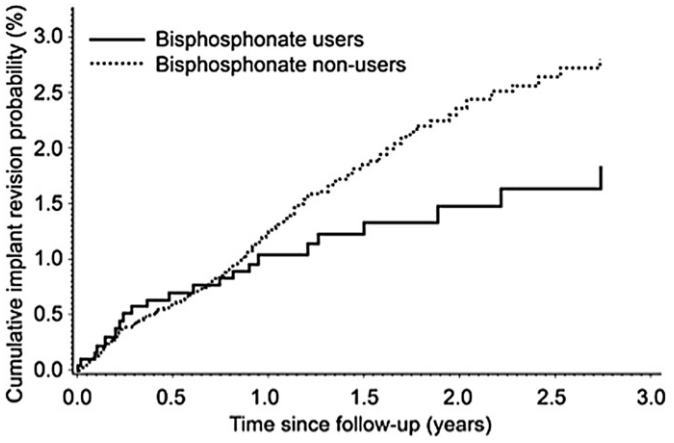
Purpose: Osteolysis and aseptic loosening are the most common cause of revision arthroplasty worldwide. Bisphosphonates might improve implant survival through their anti-osteoclast effects. We aimed to study the association between bisphosphonate use and implant survival.

Methods: A retrospective cohort study was conducted within the Danish nationwide registries (5.5 million residents). We identified patients aged >=40 years undergoing total joint replacement (TJR) during the study period (1998-2007) using ICD10 codes. Patients with inflammatory arthritides, bone Paget, hip fracture and use of DMARDs were excluded. Each participant was followed up until end of study, date of emigration, revision surgery, or patient's death, whichever came first. Participants were classified as bisphosphonate users (BPU) if they had been on treatment for at least 6 months. A time-varying exposure was used to avoid immortal-time bias. Up to six BP non-users (BPNU) undergoing arthroplasty were matched to each BPU using propensity scores. Stratified Cox regression was used to model implant survival according to bisphosphonate use. Further, we studied the association between duration of use, adherence (medication possession ratio=MPR), and timing of therapy initiation (pre-op vs post-op) and implant survival. Finally, we tested for a-priori defined interactions

between BP use and age, sex, joint replaced (hip/knee), and prior fracture on outcome by introducing multiplicative terms in the equation.
Results: 80,342/95,392 (84.2%) subjects were eligible. We identified 1,950 (2.4%) BPU, and 1,911 (98.0%) of them were matched to 10,755 BPNU. In total, 226/12,666 (1.78%) of the participants (22/1,911 BPU and 204/10,755 matched BPNU) underwent revision surgery during study follow-up (median 1.11 years, inter-quartile range 0.43-2.29 years).
Cox regression models showed reduced revision risk in BP users (propensity-matched HR 0.59; 95% Confidence Interval (CI) [0.37-0.94]) [Figure], which remained significant after multivariable adjustment for unbalanced covariates (adjusted HR 0.59; 95% CI [0.37-0.93]). This protective effect was only seen in BPU who initiated treatment post-operatively (adjusted HR 0.36 ; 95% CI [0.15-0.84]) and not in those starting pre-op (adjusted HR 0.77; 95% CI [0.44-1.35]), and who remained on treatment for at least one year: adjusted HR 0.50; 95% CI [0.27-1.00] for those treated for 1-2 years compared to adjusted HR 1.29; 95% CI (0.80-2.08) in those treated for 6-12 months. Patients with the highest adherence benefited the most (adjusted HR 0.53; 95% CI (0.30-0.95)) in BPU with MPR>0.8).
The effect of BPU on implant survival was not modified by age, gender, fracture history or joint replaced (all p for interactions>0.2).
Conclusions: BPU are at 40% reduced risk of revision compared to matched BPNU. These results are similar to previous findings using similar retrospective data from the UK [Prieto-Alhambra D et al. BMJ 2011]. Confirmation of these beneficial effects in formal randomized controlled trials is urgently needed.



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ASSOCIATION OF BIOMARKERS WITH OSTEOARTHRITIS PROGRESSION BASED ON MRI: RESULTS FROM THE VANCOUVER KNEE OSTEOARTHRITIS PROGRESSION (KOAP) STUDY

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Purpose: To determine the association of biomarkers with progression of osteoarthritis (OA), based on MRI, in a population-based cohort of predominantly pre-radiographic disease.
Methods: Population-based longitudinal cohort study of subjects, age 40 to 79, with knee pain. Subjects were evaluated at baseline and follow-up (FU) using detailed clinical assessments, knee x-ray, MRI (1.5T) and biomarkers. MRI of cartilage (MRC) was scored 0-4 on six joint surfaces. Progression was defined on MRI as an increase in MRC score of $\geq$1 grade on at least 2 cartilage surfaces or an increase of MRC score of $\geq$2 grades on at least 1 cartilage surface. Urine biomarkers included C-telopeptide of type II collagen (uCTX-II) (Nordic Bioscience), type II and type I and II collagen cleavage neoepitopes (uC2C, uC1,2C) (Ibex), N-telopeptide of type I collagen (uNTX-I) (Ostex). Serum biomarkers included sC1,2C, sC2C, c-propeptide of type II procollagen (sCPII), 846 epitope (sCS846) (Ibex), cartilage oligomeric matrix protein (sCOMP) (AnaMar) and hyaluronic acid (sHA) (Corgenix). Ratios of type II collagen degradation with synthesis markers were also evaluated. Biomarker data were log transformed. Exponential regression analysis was used to determine the association of each biomarker with OA progression, adjusted for age, gender, BMI and joint count. All analyses utilized longitudinal stratum sampling weights to ensure generalizability of results.
Results: Of 255 subjects seen at baseline, 163 (63.9%) were assessed at a median FU of 3.2 years (range 2.5-5.1). Of these, 60.6% had KL grade <2, mean age was 57.6 years. MRI progression was present in 15.5% of subjects. Biomarkers significantly associated with OA progression included uCTX-II (HR 2.28; 95% CI 1.00, 5.16), sCPII (HR 0.58; 95% CI 0.34, 0.99), as well as ratios of uCTX-II/sCPII (HR 1.78; 95% CI 1.17, 2.72), uC1,2C/sCPII (HR 1.52; 95% CI 1.08, 2.16) and sC2C/sCPII (HR 2.15; 95% CI 1.05, 4.39) (Table 1).

Table 1

Biomarkers	Hazard Ratio (95% CI)
uNTX-I	**1.80 (0.83, 3.90**
uCTX-II	2.28 (1.00, 5.16)
uC2C	1.06 (0.57, 1.97)
uC1,2C	1.29 (0.88, 1.89)
sHA	1.44 (0.79, 2.63)
sCS846	**1.32 (0.49, 3.56)**
sCPII	0.58 (0.34, 0.99)
sCOMP	2.58 (0.48, 13.90)
sC2C	0.53 (0.15, 1.87)
sC1,2C	**1.61 (0.52, 4.94)**
uCTX-II/sCPII	1.78 (1.17, 2.72)
uC2C/sCPII	**1.44 (0.93, 2.21)**
uC1,2C/sCPII	**1.52 (1.08, 2.16)**
sC2C/sCPII	2.15 (1.05, 4.39)

Conclusions: In this population-based cohort of predominantly pre-radiographic knee OA, uCTX-II and sCPII were both significantly associated with OA progression. As well, ratios of uCTX-II/sCPII, uC1,2C/sCPII and sC2C/sCPII were significantly associated with OA progression with similar strengths of association. These biomarkers may be useful in future studies aimed at evaluating OA disease progression in epidemiologic studies and clinical trials.

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SIMPLIFIED CLINICAL PREDICTION MODEL FOR OSTEOARTHRITIS PROGRESSION BASED ON MRI: RESULTS FROM THE VANCOUVER KNEE OSTEOARTHRITIS PROGRESSION (KOAP) STUDY

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Purpose: To determine the clinical predictors of osteoarthritis (OA) progression based on cartilage damage on MRI in a population-based cohort of predominantly pre-radiographic knee OA and to develop a simplified model to identify those at risk of progression with high specificity for practical application in clinical trials.
Methods: Population-based longitudinal cohort study of subjects, age 40 to 79, with knee pain. Subjects were evaluated at baseline and follow-up (FU) using detailed clinical assessments, standardized knee examination, fixed-flexion knee x-ray and MRI (1.5T). X-rays were read for Kellgren-Lawrence (KL) 0-4 grade. MRI of cartilage (MRC) was scored 0-4 on six joint surfaces by a blinded reader. OA progression was defined on MRI as an increase in MRC score of $\geq$1 grade on at least 2 cartilage surfaces or an increase in MRC score of $\geq$2 grades on at least 1 cartilage surface. Exponential regression analysis was used to develop a prediction model for OA progression. The model was evaluated based on prediction accuracy, Akaike's Information Criterion (AIC) and C-index, where a 1.0 score indicates a perfect model fit. The model was then simplified by removing variables and evaluating the impact on the model accuracy and C-index. All analyses utilized longitudinal stratum sampling weights to maintain generalizability.
Results: Of 255 subjects seen at baseline, 163 (63.9%) were assessed at a median FU of 3.2 years (range 2.5-5.1). Of these, 60.6% had KL grade